Clinical Study Report Synopsis

Drug Substance	Saxagliptin
Study Code	D1680C00005
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A 24-Week International, Multi-centre, Randomized, Parallel-group, Double-blind, Placebo-controlled, Phase III Study to Evaluate the Efficacy and Safety of Saxagliptin in Adult Patients with Type 2 Diabetes who have Inadequate Glycaemic Control with Diet and Exercise

Study dates: First subject enrolled: 27 June 2008
Last subject last visit: 03 October 2009

Phase of development: Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study center(s)

This study was conducted at 40 centers in the following countries: China (19 sites), India (8 sites), The Philippines (7 sites), and South Korea (6 sites).

Publications

None at the time of writing this report.

Objectives

The primary efficacy objective of this study was to compare, after a 24-week oral administration of double-blind treatment, the absolute change from baseline in glycosylated hemoglobin (HbA1c) achieved with saxagliptin versus placebo in treatment-naïve patients with type 2 diabetes who have inadequate glycemic control with diet and exercise alone.

Three key secondary objectives were to compare the effects of saxagliptin versus placebo after a 24-week double-blind treatment for the following:

- The change from baseline in fasting plasma glucose (FPG)
- The change from baseline in the area under the curve (AUC) from 0 to 180 minutes for postprandial glucose (PPG) during a mixed meal (instant noodles) tolerance test (MMTT) on a subset of approximately 100 patients
- The proportion of patients achieving a therapeutic glycemic response defined as HbA1c <7.0%

Other efficacy objectives were to compare the effects of saxagliptin versus placebo after a 24-week double-blind treatment for the following:

- The change from baseline in the incremental AUC from 0 to 180 minutes for PPG during an MMTT on a subset of approximately 100 patients*
- Change from baseline in mixed meal insulin sensitivity model (MMIS) on a subset of approximately 100 patients**
- Change from baseline in β-cell function and insulin sensitivity (as measured by homeostasis model assessment [HOMA-2])**
- The change from baseline in fasting insulin, C-peptide, glucagon, proinsulin, and proinsulin/insulin ratio
- The change from baseline in area AUC from 0 to 180 minutes for postprandial insulin, C-peptide, and glucagon during an MMTT on a subset of approximately 100 patients

- The change from baseline in body mass index (BMI), waist circumference, and body weight
- The proportion of patients achieving a glycemic response for each category as defined below:
  - HbA1c ≤6.5%
  - Reduction in HbA1c ≥0.5%
  - Reduction in HbA1c ≥0.7%
  - FPG <6.1 mmol/L (110 mg/dL)
  - FPG <7.0 mmol/L (126 mg/dL)
  - 120-minute PPG <7.8 mmol/L (140 mg/dL)
  - 120-minute PPG <11.1 mmol/L (200 mg/dL)
- Percent change from baseline in fasting lipids: total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C) and triglycerides (TG)
- Change from baseline in 120-minute PPG during MMTT**
- Change from baseline in glucose excursion during MMTT**

*Incremental AUC for PPG (0 to 180 minutes) was the baseline-subtracted net increase in AUC PPG for this time interval.

**As changes from the protocol to the planned analyses (Section 5.8.2), the Matsuda index (for insulin sensitivity) and insulinogenic index (for early insulin secretion) were added as variables in place of the MMIS for the subset of subjects for whom an MMTT was conducted. The change from baseline in insulin sensitivity was deleted (only change from baseline β-cell function was to be calculated), and variables for glucose excursion and 120-minute PPG during MMTT were added.

Safety and tolerability were evaluated by assessment of AEs (including AEs of special interest), hypoglycemic events, laboratory values, ECGs, pulse, blood pressure (BP), weight, and physical examination.

Study design

This study was a 24-week, international, multicenter, randomized, parallel-group, double-blind, placebo-controlled Phase 3 study to evaluate the efficacy and safety of saxagliptin in adult subjects with type 2 diabetes who have inadequate glycemic control with diet and exercise. The study comprised an enrollment period, a 4-week placebo lead-in period, and a 24-week randomized treatment period. Subjects with lack of adequate glucose control during

the randomized treatment period were eligible for the addition of open-label metformin as a rescue from continued hyperglycemia. Pre-specified glycemic parameters based on FPG were established during the double-blind treatment phase. This multinational study was performed to evaluate the efficacy and safety of saxagliptin in the Asian population in the Asian Pacific region, in particular, China. The results of the analysis of the China cohort of this multinational study are presented in a separate clinical study report (hereafter referred to as the "China supplement").

Target subject population and sample size

Men or women who were ≥18 years of age diagnosed with type 2 diabetes with inadequate glycemic control (HbA1c ≥7.2% and ≤10.0%), had a fasting C-peptide level ≥ 0.33 nmol/L (≥1 ng/mL), and who were drug naïve were eligible for enrollment. After a 4-week placebo lead-in period with diet and exercise, subjects with HbA1c≥7.0% and ≤10.0% were eligible for treatment randomization.

With a total of 530 subjects randomized and treated (or 265 per treatment group), there would be 98% power to detect a 0.5% difference between the 2 randomized treatment groups in absolute change from baseline to Week 24 in HbA1c at the 5% level, assuming a standard deviation of change from baseline in HbA1c of 1.2%.

For the China cohort, a total of 308 subjects were expected to be randomized (approximately 154 per treatment arm). The sample size for the China cohort also assumed about a 20% dropout rate. The sample size of 308 subjects would be sufficient for a 90% power to detect a 0.5% difference between the 2 randomized treatment groups in absolute change from baseline to Week 24 in HbA1c, assuming a standard deviation of change from baseline in HbA1c of 1.2%. The remaining 222 subjects were to be allocated to approximately 102 from India, approximately 40 from Korea, and approximately 80 from the Philippines.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Study drug: Saxagliptin tablets 5 mg (batch number H 2024-01-01-01) for oral administration once daily in the morning.

Control drug: Placebo tablets matching saxagliptin 5 mg (batch numbers H 2014-01-01-02, H 2014-01-01-03) for oral administration once daily in the morning.

The investigational products (IPs) were to be taken at approximately the same time each day during the study period. For all visits, the subjects were required to visit the study center in the morning without taking the IP. Subjects were instructed to abstain from all food for 8 hours prior to each clinical visit; however, drinking water was allowed.

Duration of treatment

The total duration of treatment with study drug was 24 weeks. Subjects received placebo in a single-blind fashion for a 4-week placebo lead-in period, followed by the 24-week, double-blind treatment period, in which subjects received saxagliptin 5 mg or placebo for comparator.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

The primary variable for the study was the change from baseline to Week 24 in HbA1c.

The key secondary variables were:

- Change from baseline to Week 24 in FPG
- Change from baseline to Week 24 in PPG AUC (0 to 180 minutes) during MMTT
- Proportion of patients achieving a therapeutic glycemic response defined as HbA1c <7.0% at Week 24

Other secondary efficacy variables were:

- Change from baseline in incremental PPG AUC (0 to 180 minutes) during MMTT
- Change from baseline in Matsuda index and insulinogenic index
- Change from baseline in β-cell function (as measured by HOMA-2)
- Change from baseline in fasting insulin, C-peptide, glucagon, proinsulin, and proinsulin/insulin ratio
- Change from baseline in AUC for insulin, C-peptide, and glucagon as well as change from baseline in 120-minute PPG and in glucose excursion following an MMTT
- Change from baseline in BMI, waist circumference, and body weight
- Proportion of subjects achieving a therapeutic glycemic response defined as: HbA1c ≤6.5%; reduction in HbA1c ≥0.5%; reduction in HbA1c ≥0.7%; FPG <6.1 mmol/L (110 mg/dL); FPG <7.0 mmol/L (126 mg/dL); 120-minute PPG <7.8 mmol/L (140 mg/dL); and 120-minute PPG <11.1 mmol/L (200 mg/dL)
- Change from baseline in TC, LDL-C, HDL-C and TG

Criteria for evaluation - safety (main variables)

Safety and tolerability were evaluated by assessment of AEs (including AEs of special interest), hypoglycemic events, laboratory values, ECGs, pulse, BP, weight, and physical examination.

Statistical methods

Data recorded on or after rescue medication were excluded from all analysis of efficacy data. The missing Week 24 efficacy endpoints were replaced by the last observed value prior to rescue medication after baseline.

The primary analysis for efficacy variables was based on the Full analysis set, which included subjects who took at least 1 dose of IP and had both baseline and post-baseline efficacy data. A sensitivity analysis was to be performed based on the Per Protocol (PP) analysis set, (subjects in the Full analysis set who had no reason for exclusion), only if more than 10% of the subjects in any treatment group were found to deviate significantly from the terms and conditions of the protocol. Otherwise, analysis of and inference to the primary efficacy variable, demographics, and baseline diabetes-related characteristics were restricted to the Full analysis set. If PP analysis was deemed necessary, then the analysis was to be performed on the primary variable (change from baseline in HbA1c at Week 24), demographics, and baseline diabetes-related characteristics only. The analysis of MMTT included participants in that test only. (Note: All MMTT participants were subjects enrolled in China.)

All statistical analyses were performed using Version 8 (or higher) of SAS®.

The primary efficacy analysis was to compare saxagliptin with placebo for the absolute change from baseline in HbA1c to Week 24, analyzed on the Full analysis set using an analysis of covariance (ANCOVA) model. The model used absolute change from baseline as a dependent variable, treatment and country as fixed main effects, and baseline HbA1c as a covariate. Within the framework of the ANCOVA model, point estimates and the 2-sided 95% confidence intervals (CIs) for the mean change within each treatment group, as well as for the differences in mean change between the saxagliptin treatment arm and the placebo treatment arm, were presented.

To assess the robustness of the primary efficacy analysis, the modelling of the primary analysis was repeated utilizing repeated measures analysis (using mixed model). This model contained terms for treatment group, baseline measurement, country, time, and time by treatment group. Subgroup analyses for the primary efficacy variable included country, gender (male, female); age (<65 years, ≥65 years, and ≥75 years); baseline (Week 0) HbA1c (<8.0%, ≥8.0% to <9.0%, and ≥9.0%); duration of type 2 diabetes since diagnosis (≤1.5 years, ≤3 years, >3 years to <5 years, ≥5 years, and ≥10 years); and baseline BMI (<30 kg/m^2 and ≥30 kg/m^2).

Three important secondary efficacy endpoints were identified for significance testing with the overall primary endpoints in a fixed-sequence testing procedure. The order of these key secondary efficacy endpoints and the associated statistical methods for each were:

1. Change from baseline to Week 24 in FPG; ANCOVA similar to the model used for the primary endpoint using the Full analysis set

2. Change from baseline to Week 24 in AUC (0 to 180 minutes) in PPG during MMTT; ANCOVA similar to the model used for the primary endpoint using the Full analysis set on a subset of approximately 100 subjects.

3. The treatment dependency of proportion of subjects achieving a therapeutic glycemic response defined as HbA1c <7.0%, discriminated by 2-sided Fisher's Exact test using the Full analysis set

Statistical inferences started from the overall primary efficacy endpoint. If saxagliptin was superior in change from baseline in HbA1c compared to placebo, then statistical inference continued with the first secondary efficacy endpoint (1); otherwise, statistical inference of the overall efficacy endpoints was to stop. The p-values that followed could not be considered as significant in this confirmatory analysis when the fixed sequence procedure was used to control the overall type 1 error rate, even if the p-value was less than 0.05. Similarly if saxagliptin was superior in change from baseline in FPG compared to placebo, then statistical inference continued with the second secondary efficacy endpoint (2); otherwise, statistical inference of the overall efficacy endpoints was to stop. Similar statistical inference was followed with the prescribed order (1) to (3) with the same decision rule until all 3 secondary endpoints were analyzed or interrupted at any non-significant finding. These same secondary efficacy endpoints were analyzed by country using the same method as described. Point estimates and 2-sided 95% CIs were presented for each endpoint by country.

The other efficacy variables were analyzed similarly.

All comparisons were 2-sided at the 5% significance level.

For all safety variables, the primary safety analyses excluded data collected on or after rescue medication. Sensitivity analyses on all data collected regardless of rescue up to and including Week 24 utilizing the Safety analysis set were performed for selected AE analyses and selected laboratory analyses. Analysis for safety and tolerability endpoints were summarized by descriptive statistics or frequency tables and/or graphic method. There were no hypotheses proposed a priori for these safety endpoints.

All efficacy analyses and safety summaries described above were also repeated for the China cohort only and are reported separately.

Subject population

A total of 568 subjects were randomized and treated with either saxagliptin (n=284) or placebo (n=284). The proportions of subjects in the Randomized analysis set who completed the 24-week, double-blind, randomized treatment period (regardless of rescue) were high (90% overall), and similar between the 2 treatment groups (92.3% vs 87.3%). The proportions of subjects who completed without receiving rescue medication were higher in the saxagliptin group compared with the placebo group (87.3% vs 77.8%). The proportions of subjects discontinuing study treatment (regardless of rescue) due to study-specific discontinuation criteria during double-blind treatment were similar overall between the 2 treatment groups (n=3, 1.1% in the saxagliptin group and n=4, 1.4% in the placebo group). The most common reason for discontinuation in both treatment groups was subject withdrawal of consent (n=11, 3.9% in the saxagliptin group and n=23, 8.1% in the placebo group). A smaller proportion of subjects in the saxagliptin group compared with placebo received rescue medication during the randomized treatment period (5.28% vs 10.21%).

Baseline demographic and diabetes characteristics were generally well balanced across the 2 treatment groups in the Randomized, Full, and MMTT analysis sets and were representative

of treatment-naïve subjects with type 2 diabetes with inadequate glycemic control with diet and exercise alone. In the Randomized analysis set, of the 568 randomized and treated subjects, 55.5% were male and the mean age was 51 years (range: 20 to 80 years). A total of 54 (9.5%) subjects were ≥ 65 years of age and 6 (1.1%) were ≥75 years of age. Mean body weight was 69 kg (range: 35 kg to 113 kg). Approximately 13% of the study population had a mean BMI ≥30.0 kg/m^2. Similar proportions of subjects in each treatment group were diagnosed with type 2 diabetes ≤3 years (89.8% overall) and ≥5 years (4.9% overall) before the start of the study; the median duration of diabetes was 0.2 years in the overall population. The mean baseline HbA1c in the Randomized analysis set was 8.1% in the saxagliptin group and 8.2% in the placebo group. There were no clear differences between the saxagliptin and placebo groups with regard to the use of specific concomitant medications. Thus, it was unlikely that concomitant medications had any effect on the results of the study. The observed levels of compliance were similar among the 2 treatment groups and therefore were unlikely to have any effect on the results of the study. The majority of subjects in the study achieved ≥80% and ≤120% treatment compliance for IP (saxagliptin [96.1%] and placebo [97.5%]).

Summary of efficacy results

Table S1 summarizes the change in HbA1c from baseline to Week 24 of randomized treatment for the Full analysis set (last observation carried forward [LOCF]) (the primary analysis).

Mean baseline HbA1c values were similar in the 2 treatment groups. There was a mean decrease in HbA1c at Week 24 in both treatment groups. Adjusted mean changes from baseline to Week 24 were -0.84% for the saxagliptin group and -0.34% for the placebo group. Based on the difference in adjusted mean changes from baseline, treatment with saxagliptin significantly decreased HbA1c compared with placebo. The difference in adjusted mean changes between the 2 groups (saxagliptin minus placebo) was -0.50% (2-sided 95% CI -0.65% to -0.34%; $p<0.0001$).

Similar results were obtained in the Full analysis set using observed values and in the repeated measures analysis.

Table S1 Change in HbA1c from baseline to Week 24 (LOCF) (Full analysis set)

HbA1c[a]	Saxa (N=280)	Placebo (N=280)
n	277	274
Units: %		
Baseline mean (SE)	8.15 (0.050)	8.14 (0.050)
Week 24 mean (SE)	7.25 (0.063)	7.75 (0.076)
Mean change from baseline (SE)	-0.90 (0.053)	-0.39 (0.060)
Adjusted change from baseline		
Mean (SE)	-0.84 (0.067)	-0.34 (0.065)
2-sided 95% CI	-0.97, -0.71	-0.47, -0.21
Difference vs placebo		
Mean (SE)[b]	-0.50 (0.079)	NA
2-sided 95% CI	-0.65, -0.34	NA
P-value	<0.0001	

Baseline is defined as the last assessment within 42 days before the first dose of double-blind study drug, and before or including the first Day 1 assessment.
ANCOVA model: post - pre = pre + treatment + country.
[b] Estimate = adjusted mean change for saxagliptin – adjusted mean change for placebo.
ANCOVA Analysis of covariance; CI Confidence interval; HbA1c Glycosylated hemoglobin; LOCF Last observation carried forward; NA Not applicable; Saxa Saxagliptin; SE Standard error.

Key secondary efficacy findings included:

- Saxagliptin resulted in a significant reduction in FPG compared with placebo at Week 24 (adjusted mean difference of -0.73 mmol/L [-13.12 mg/dL]; 2-sided 95% CI -1.06 to -0.39 mmol/L [-19.12 to -7.13 mg/dL]; p<0.0001).
- Saxagliptin resulted in a significant reduction in PPG AUC compared with placebo following an MMTT at Week 24 (adjusted mean difference of -182 mmol•min/L [-3280 mg•min/dL]; 2-sided 95% CI -289 to -74 mmol•min/L [-5214 to -1345 mg•min/dL]; p=0.0010).
- Saxagliptin resulted in a significantly greater proportion of subjects achieving therapeutic glycemic response defined by HbA1c <7% at Week 24 compared with placebo (45.8% and 28.8%, respectively; adjusted mean difference of 17.0%; 2-sided 95% CI 8.9% to 24.9%; p<0.0001).

Other efficacy findings included:

- Saxagliptin resulted in numerically greater reductions compared with placebo in:
    - incremental PPG AUC (0 to 180 minutes) during MMTT (adjusted mean difference of -185 mmol•min/L [-3342 mg•min/dL]; 2-sided 95% CI -255 to -115 mmol•min/L [-4594 to -2090 mg•min/dL]),
    - 120-minute PPG during MMTT (adjusted mean difference of -1.32 mmol/L [-23.75 mg/dL]; 2-sided 95% CI -2.08 to -0.56 mmol/L [-37.45 to -10.06 mg/dL],
    - glucagon AUC (0 to 180 minutes) during MMTT (adjusted mean difference of -155 pmol•min/L [-523 pg•min/mL]; 2-sided 95% CI -409 to 99 pmol•min/L [-1401 to 355 pg•min/mL]), and
    - fasting insulin (adjusted mean difference of -7.0 pmol/L [-1.0 μU/mL]; 2-sided 95% CI -20.4 to 6.4 pmol/L [-2.9 to 0.9 μU/mL]); fasting proinsulin (adjusted mean difference of -1.4 pmol/L; 95% CI -4.6 to 1.8 pmol/L); and fasting proinsulin/insulin ratio (adjusted mean difference of -5.3%; 95% CI -10.4 to -0.3%).
- Saxagliptin resulted in numerically greater increases compared with placebo in:
    - C-peptide AUC (0 to 180 minutes during MMTT) (adjusted mean difference of 33.1 nmol•min/L [100.2 ng•min/mL]; 95% CI 12.5 to 53.7 nmol•min/L [37.9 to 162.6 ng•min/mL]), and
    - insulin AUC (0 to 180 minutes) during MMTT (adjusted mean difference of 3578.7 pmol•min/L [515.0 μU•min/mL]; 95% CI -289.8 to 7447.2 pmol•min/L [-41.9 to 1071.9 μU•min/mL]).
- There were no apparent differences between treatment groups in fasting C-peptide or fasting glucagon at Week 24.
- There was a numerically greater increase in calculated fasting β-cell function (HOMA-2β) in the saxagliptin group compared with the placebo group. A numerically greater increase in calculated early insulin secretion (60-minute insulinogenic index) during MMTT was also seen in the saxagliptin group compared with the placebo group. Calculated insulin sensitivity (Matsuda index) increased during MMTT in both treatment groups with no apparent difference between treatment groups.
- In general, the proportions of subjects achieving a glycemic response, as defined by various HbA1c, FPG, and 120-minute PPG response thresholds, were numerically higher in the saxagliptin group compared with the placebo group.

- Reductions in body weight (-0.32 kg for saxagliptin and -1.14 kg for placebo; difference in the adjusted mean change from baseline of 0.82 kg, 2-sided 95% CI 0.39 to 1.25 kg) and BMI were observed in both treatment groups. No apparent changes were seen in waist circumference in either treatment group.

- There was an increase in fasting TG in both treatment groups (10.7% for saxagliptin and 6.0% for placebo); small changes were seen in both treatment groups in TC, HDL-C, and LDL-C.

- Saxagliptin resulted in numerically smaller glucose excursions at 60-, 120-, and 180-minutes during MMTT compared with placebo.

Summary of safety results

The mean duration of exposure including rescue was longer in the saxagliptin group compared with placebo (160 vs 156 days). The majority of subjects (87.0% and 82.0% of subjects, respectively) were exposed to treatment (regardless of interruption and regardless of rescue) for ≥166 days.

The mean duration of exposure excluding days on or after rescue medication was 9 days longer in the saxagliptin group compared with the placebo group (156 vs 147 days). The proportions of subjects exposed to treatment for ≥166 days (regardless of interruption and excluding days on or after rescue medication) were 82.4% and 73.2% in the saxagliptin and placebo groups, respectively.

The overall proportions of subjects with AEs during the 24-week randomized treatment period, excluding AEs reported on or after rescue medication, were 43.7% in the saxagliptin group and 35.9% in placebo group. The difference between treatments in the overall incidence of AEs may be explained in part by the longer mean exposure to randomized treatment in the saxagliptin group (9 more days when days on or after rescue medication were excluded) compared to the placebo group. The system organ class (SOC) with the highest number of subjects with AEs in both treatment groups was Infections and Infestations with 45 (15.8%) subjects in each group. At the preferred term (PT) level, the most common AE with an incidence of ≥2% in the saxagliptin group and greater than placebo within the SOC of Infections and Infestations was nasopharyngitis (3.2% and 2.8%). Other SOCs with an incidence of ≥5% in the saxagliptin group and greater than placebo were Gastrointestinal Disorders (11.3% and 5.6% in the saxagliptin and placebo groups, respectively) and Musculoskeletal and Connective Tissue Disorders (6.3% and 4.2%, respectively). At the PT level within the SOC of Gastrointestinal Disorders, there were 9 (3.2%) subjects with diarrhea in the saxagliptin group and 4 (1.4%) in the placebo group; the additional events were single cases with various PTs. There were no events at the PT level with an incidence of ≥2% and greater than placebo within the SOC of Musculoskeletal and Connective Tissue Disorders. There was one death during the study due to a myocardial infarction in the saxagliptin group. The incidence of SAEs, excluding SAEs reported on or after rescue medication was low in both treatment groups, but numerically higher in the saxagliptin group compared with the placebo group (8 [2.8%] vs 4 [1.4%]). The only SOC with more than one SAE was Cardiac in

the saxagliptin group and Infections and Infestations in the placebo group. The incidence of discontinuations of IP due to AEs (excluding AEs reported on or after rescue medication) was low and similar between the 2 treatment groups (3 [1.1%] vs 2 [0.7%]); one of these (in the placebo group) was due to an SAE.

The proportions of subjects experiencing an AE indicative of an acute cardiovascular event were low (1.4% for saxagliptin and 0.4% for placebo). The proportions of subjects with hypoglycemic events were low and similar between treatment groups. Few subjects had AEs of lymphopenia, thrombocytopenia, selected skin-related AEs, localized edema, hypersensitivity, or fracture, and no subjects had an AE of pancreatitis.

The numbers of subjects with marked laboratory abnormalities (regardless of rescue) were low in both treatment groups. More subjects had markedly abnormal lymphocyte results in the saxagliptin group compared to the placebo group (4 vs 0 for saxagliptin and placebo, respectively).

Small mean reductions in systolic and diastolic BP were observed in both treatment groups. At Week 24, mean changes from baseline for systolic BP were -5.31 and -7.29 mmHg, in the saxagliptin and placebo groups, respectively, and, for diastolic BP, were -4.00 and -3.95 mmHg, respectively.

There were no clinically relevant changes in mean values for any hematology or clinical chemistry laboratory parameters, and the numbers of subjects experiencing marked laboratory abnormalities were low in both treatment groups. There were no apparent treatment-related effects on changes in physical findings, vital signs, or ECGs in either treatment group. Both treatment groups had small reductions in systolic and diastolic BP after 24 weeks of treatment.

No differences in the safety conclusions were drawn based on data including post-rescue information.